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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/903,396	07/10/2001	Keith D. Allen	R-359	9463

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EXAMINER
BERTOGLIO, VALARIE E

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/12/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,396	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-4,13-16,30-32,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-12,17-29 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

Application No.: 09903396

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The sequence in Figure 2A requires a SEQ ID NO to be stated either in the Figure or in the brief description of the drawing..

If Necessary, Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE

Election/Restrictions

Applicant's election with traverse of Invention III, claims 8, 17-23,25 and 33 in paper No. 10, dated 02/10/2003 is acknowledged. It has been determined that it would not require undue burden on the part of the examiner to examine Groups II-V together. While the restriction on the basis that the claimed inventions are patentably distinct is still held proper, Groups II-V have been rejoined in this action.

The traversal is partially on the ground(s) that a search of Invention I claims and Invention II-VII or Invention VIII claims together would not be an undue burden because a reasonable search would produce results related to the targeting construct of Invention I and the cells of Invention II or the animals of Invention III or the methods of screening using the transgenic animal of Invention IV, or the methods of making a transgenic animal of Invention V, or the methods of screening using the transgenic cells of Invention VI, the agents of Invention VII, or the database of Invention VIII. This argument is not found persuasive because it is maintained that each of the inventions of Invention I and Invention II-VII or VIII require a separate search status on the basis of each of Inventions II-VIII requiring a materially different product from that of Invention I, which is separately classified. In particular, Invention I is directed to methods of making a gene targeting construct that is not necessary to disrupt the glucocorticoid induced receptor in cells or in animals. Materially different constructs can be used to disrupt the glucocorticoid induced receptor. Furthermore, the nucleic acid sequences of Invention I and the cells of Invention II or the animals of Invention III are structurally and functionally different and have different uses. As such, Invention I and Invention II or Invention III require materially different reagents and technical considerations such that a proper search for both inventions would require an extensive search for materially different methods thereby placing an undue search burden upon the Examiner. Furthermore, the nucleic acid of Invention I

and the agents of Invention VII and the database of Invention VIII are structurally and functionally distinct. The nucleic acid is not required for the compounds or the database and the compounds or database are not necessary for the nucleic acid. The nucleic acid is not necessary for the methods of Inventions IV, V or VI. The cells, the animal and the modulators and the methods of using said products have distinct and different purposes from the nucleic acid construct. Therefore, it is maintained that the Invention I and Invention II-VII or VIII are distinct due to distinct structures, classification and method steps and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of the cells of Invention II or the transgenic animals of Invention III and the methods of identifying agents of Invention VI or the agent of Invention VII together would not be an undue burden. The examiner maintains that Invention II or III and Invention VI or VII are patentably distinct. The cells of Invention II can be used to make the animals of Invention III and are not restricted to the distinct use of Invention VI and the methods of Invention VI do not utilize the animals of Invention III. The cells or animals are structurally and functionally distinct from the compounds of Invention VII and the cells or animals each have a distinct and different purpose from the compounds. The cells or animals can be used for in vitro assays, to study function of glucocorticoid-induced receptor, to produce proteins, or to test gene expression while the compounds can be used to modulate gene expression. The examiner maintains that Inventions II or III and Inventions VI or VII are structurally and functionally distinct, have different purpose and use, and are classified differently. Furthermore, the burden required to search the cells or animals with the compounds, which have a different classification, would be undue.

The traversal is partially on the ground(s) that a search of Invention II or III and the database of Invention VIII together would not be an undue burden. The cells of Invention II and

the animals of Invention III can be used to screen agents, while the database of Invention VIII can be used for statistical analysis. Neither the cells nor the animals are necessary for the database and the database is not necessary for the cells or animals. The cells and animals and the database are classified separately and the burden required to search Inventions II or III and VIII together would be undue.

The traversal is partially on the ground(s) that a search of Invention IV,V or VI and the agent of Invention VII together would not be an undue burden. The examiner maintains that Invention IV, V or VI and Invention VII are patentably distinct because the methods of using a transgenic animal of Invention IV, the methods of making a transgenic animal of Invention V, the methods of using cells to screen for modulators of Invention VI do not require the agent of Invention VII and the agent does not require any of Inventions IV,V or VI. Furthermore, the burden required to search the Inventions IV,V or VI with the agent of Invention VII, which has a different classification, would be undue.

The traversal is partially on the ground(s) that a search of Invention IV,V or VI and the database of Invention VIII together would not be an undue burden. The examiner maintains that Invention IV, V or VI and Invention VIII are patentably distinct because the methods of Inventions IV, V, or VI do not require the database of invention VIII and the database does not require the methods. The burden required to search inventions IV, V, or VI and Invention VIII together would be undue.

The traversal is partially on the ground(s) that a search of Inventions V and VI together would not be an undue burden. The examiner maintains that the methods of making a transgenic animal of Invention V and the methods of using the cells of Invention VI are materially different and plurally independent. The methods steps are different and are performed with a different purpose and technical considerations and reagents. The methods of making the

animals do not require the methods steps of the methods of using the cells and vice versa. The animals and the cells are classified differently and the burden required to search Inventions V and VI together would be undue.

With exception of arguments directly pertaining to Inventions II-V, which have been rejoined, the restriction requirement is still deemed proper and is therefore made **FINAL.**

Claims 1-35 are pending, however, claims 1-4,13-16,30-32,34 and 35 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions, the requirement having been traversed in Paper No. 10. Claims 5-12, 17-29 and 33 are under current examination.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The sequence in Figure 2A requires a SEQ ID NO to be stated either in the Figure or in the Brief Description of the Drawings**. Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing." Applicant is requested to return a copy of the attached Notice to Comply with the reply. Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-12,17-29 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 5-12,17-29 and 33 encompass more than one glucocorticoid-induced receptor gene as they are drawn to "a glucocorticoid-induced receptor gene". The claims encompass any glucocorticoid-induced receptor gene that may exist in each and every species of animal. While the specification teaches that several splice forms of the glucocorticoid-induced receptor gene exist (page 2, lines 2-3), the specification teaches only one, mouse glucocorticoid-induced receptor gene (SEQ ID NO:1). Therefore, adequate written description to support the claims encompassing more than the one, disclosed glucocorticoid-induced receptor gene is lacking.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieve regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the glucocorticoid-induced receptor gene encompassed by **SEQ ID NO:1**, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 5-12, 17-29 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse or mouse cell whose genome comprises a homozygous disruption in the glucocorticoid-induced receptor gene encoded by SEQ ID NO:1 wherein said mouse exhibits signs of hyperactivity, reduced anxiety, or decreased propensity towards behavioral despair or depression and wherein the mouse is derived from the F1N1 generation (see page 53, lines 16-21), does not reasonably provide enablement for any transgenic non-human animal or a cell of any species or genetic background with a disruption of any glucocorticoid-induced receptor gene wherein said transgenic cell or animal has any phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 5-7,9 and 26 are directed to a cell comprising a disruption in the glucocorticoid-induced receptor gene. Claim 8 is directed to a non-human transgenic animal with a disruption in the glucocorticoid-induced receptor gene. Claims 10 and 24 are directed to methods of producing a transgenic mouse with a disruption in the glucocorticoid-induced receptor gene. Claims 17-23 and 33, are directed to a transgenic mouse with a disruption in the glucocorticoid-induced receptor gene, wherein the transgenic mouse exhibits hyperactivity or reduced anxiety (claims 17-21 and 33), or decreased propensity towards behavioral despair or depression (claims 17, 22-23 and 33). Claims 11, 12 and 27-29 are directed to methods of using a transgenic mouse with a disruption in the glucocorticoid-induced receptor gene to screen for modulators of glucocorticoid-induced receptor function or expression (claims 11,12) or

modulator of a phenotype associated with the disruption of the glucocorticoid-induced receptor gene (claims 27-29).

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. For example, Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). The art of transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene (Wall, 1996 Theriogenology, Vol. 45, pp. 57-68). Furthermore, transgenic animals are regarded to have within their cells, cellular mechanisms that prevent expression of the transgene, such as methylation or deletion from the genome (Kappell, 1992, Current Opinions in Biotechnology, Vol. 3, pp. 548-553). The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994, J. Biotech. Vol. 34, pages 269-287, specifically page 281).

Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron, 1997, Molec. Biol. 7, pages 253-265, specifically page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron, 1997, Molec. Biol. 7, page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the

transgene (Cameron, 1997, Molec. Biol. 7, page 256, lines 10-13). Further, Sigmund (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that due to the position of the transgene effects expression, and thus the observed phenotype (Sigmund, 2000, Arteroscler. Throm. Vasc. Biol. 20, pages 1425-1429, specifically page 1426, col. 1, parag. 1, lines 1-7). With regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann, 1997, Transg. Res. 7, pages 73-75, specifically page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4). While, the intent is not to say that transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled.

Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. Mullins (1993, Hypertension, Vol. 22, pp. 630-633) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (1990, Nature, Vol. 344, 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer (1990, Cell, Vol. 63, 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats (Mullins, 1989, EMBO J., vol. 8, pages 4065-

4072; Taurog, 1988, Jour. Immunol., Vol. 141, pages 4020-4023). Mullins (1996, J. Clin. Invest. Vol. 98, pages S37-S40) disclose that the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another. Therefore, it was unpredictable at the time of filing what gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, site of integration, were required to make a transgenic non-human mammal of interest.

The art at the time of filing also held that the phenotype of transgenic knockout mice was unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph).

The art at the time of filing further held that targeted gene insertion technology was not available for any species other than mouse. Since homologous recombination is required for gene targeting methods, embryonic stem cell technology must be available to carry out the method. Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) teach that non-mouse ES cells capable of providing germline chimeras were not available (page S38, column 1, first paragraph). Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute to the germ line in any species other than mouse (page 65).

Furthermore, other potential methods of generating transgenic embryos using homologous recombination had not been developed at the time the invention was made (McGreath, 2000, Nature, Vol. 405, pages 1066-1069; Kent-First, 2000, Nature Biotechnology, Vol. 18, pages 928-929; Dinnyes, 2002, Cloning and Stem Cells, Vol. 4, pages 81-90). Thus, at the time of filing, the phenotype of transgenic knockout mice was unpredictable and knockout animals could not be prepared for any species other than mouse.

1) The specification does not provide adequate guidance for one of skill in the art to make and use non-human transgenic animals having a disruption in the glucocorticoid-induced-receptor gene in any species other than mouse. The methods of gene targeting such as employed in the instant invention require embryonic stem cells. As stated above, the state of the art at the time of filing was that ES cell technology was not available for targeted mutagenesis in any species other than mouse. The specification discloses injecting cells comprising a disruption in the glucocorticoid-induced receptor gene into a blastocyst to generate transgenic animals (page 14, lines 25-30). However, the specification and the art at the time of filing fail to disclose any ES cells other than mouse ES cells that contribute to the germline. Therefore, the guidance offered in the specification is limited to the production of knockout mice using mouse ES cells and no teachings or guidance are offered in regard to how one would have prepared any other species of animal using targeted mutagenesis. Without such guidance, it would require undue experimentation for one of skill in the art at the time of filing to make any transgenic, non-human animal, other than mouse, with a disruption in the glucocorticoid-induced receptor gene.

2) Applicants fail to enable making and/or using a transgenic glucocorticoid-induced receptor knockout mouse having a phenotype other than hyperactivity, reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression

(claims 8,10-12). Without such guidance as to how to make and use a transgenic glucocorticoid-induced receptor knockout mouse having any and all possible phenotypes, it would require one of skill in the art at the time the invention was made, undue experimentation to make and/or use the invention as broadly claimed.

3) The specification fails to enable disrupting any glucocorticoid-induced receptor gene in a mouse or any other species or a cell other than a mouse cell. The art at the time of filing only disclosed one glucocorticoid-induced receptor gene (Harrigan, 1991, Molecular Endocrinology, Vol. 5, pages 1331-1338). The specification only teaches one glucocorticoid-induced receptor gene (SEQ ID NO: 1). The specification does not provide adequate guidance for determining any other glucocorticoid-induced receptor gene or that other glucocorticoid-induced receptor genes have the same function as the glucocorticoid-induced receptor gene disclosed. Limiting claims 5,8,10-12,17,24,27,28, 29 and 33 to a transgenic mouse or mouse cell and deleting "a" or "an" preceding "glucocorticoid-induced receptor" in claims 5,8,10-12,17,24,27,28, 29 and 33, would overcome this rejection.

4) The specification does not enable making or using any transgenic mouse comprising a disruption in the glucocorticoid-induced receptor gene wherein the mouse is of any genetic background and wherein the mice exhibit hyperactivity, reduced anxiety, decreased propensity towards behavioral despair, or decreased propensity toward depression. The state of the art at the time of filing was that the genetic background greatly influenced the performance of a mouse in the tail suspension test and it's propensity for depression (Yoshikawa, 2002, Genome Research, Vol. 12, pages 357-366, specifically page 357, col. 1, lines 18-21; Table 2). Yoshikawa discloses discrepancies between various studies that assess the effect of genetic background and sex of a mouse in their effect on immobility in the tail suspension test. Two factors thought to account for the differences are genetic drift within identical backgrounds and

the criterion used to assess immobility (page 363, column 1). Crabbe also disclosed a rigorous study of the exemplifying effects of genetic background and laboratory conditions on the variability of results using various behavioral test protocols, including the open field test (Science, 1999, Vol. 284, pages 1670-1672).

Belzung (2001, Behavioural Brain Research, Vol. 125, pages 141-149) states that there are problems inherent in using knockout animals as models of anxiety as it is known that modulation of anxiety and other emotional disorders involves multiple genes and that this phenotype can be greatly influenced by genetic background. Belzung also states that responses exhibited by knockout mice considered to be animal models of anxiety may relate to behavioral process unrelated to anxiety. Belzung emphasizes the fact that most mouse mutant models are generated by knocking out a gene in a 129 substrain of ES cells and crossing chimeric animals to C57Bl/6 mice followed by intercrosses or very few backcrosses (refer to page 146, entire paragraph bridging columns 1 and 2). This is the same protocol used in the instant invention (page 53, lines 15-21). Harrigan further states that it is "important to emphasize that such mice are animal models of a single gene dysfunction, rather than animal models of anxiety, per se" (Abstract, lines 8-10).

The knockout mice of the instant invention were generated using the same genetic backgrounds and protocols discussed by Crabbe and by Belzung (see above). Furthermore, the specification teaches significant differences in the phenotype of mutant animals based on whether the F1 generation was backcrossed to C57BL/6 or intercrossed to siblings of a mixed 129/SvEv; C57BL/6 background (page 53, line 15-page 54, line 15). The specification further states that "The discrepancy in the results observed in the Open Field and Tail Suspension Tests between generations may reflect differences in the background strains used to generate mice" (page 54, lines 13-15). Thus, it is not clear that knocking out the glucocorticoid-induced

receptor gene in any strain of mouse will result in any of the claimed phenotypes. Furthermore, based on the state of the art, it is not clear that the mice of the claimed invention exhibit any of the behavioral disorders claimed, but rather, they exhibit symptoms of the various disorders.

Therefore, the specification is only enabling for making and using transgenic mice comprising a disruption in the glucocorticoid-induced receptor gene wherein the mouse is derived from the F1N1 generation (see page 53, lines 16-21), wherein the mouse is homozygous for the glucocorticoid-induced receptor gene disruption, and wherein the mouse displays an increase in total distance traveled in the open field test relative to the wild type mouse or wherein the mouse spends an increased amount of time in the central region of the test chamber in the open field test, or wherein the mouse exhibits less time immobilized in the tail suspension test.

5) The specification does not enable making a mouse that is heterozygous for a disruption the glucocorticoid-induced receptor gene with the phenotypes encompassed by claims 17-23. As set forth in the art, the phenotype of a transgenic, knockout animal was unpredictable at the time of filing. The specification does not teach how to make a mouse heterozygous for a disruption in the glucocorticoid-induced receptor gene that displays any phenotypes other than wildtype. Thus, the specification does not overcome the unpredictability inherent in generating knockout mice such that any phenotype in heterozygous glucocorticoid-induced receptor knockout mice could be obtained. Without such guidance, it would require one of skill in the art at the time the invention was made, undue experimentation to determine how to obtain make a mouse that is heterozygous for a disruption the glucocorticoid-induced receptor gene with the phenotypes claimed in claims 17-23 and 33.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-12,17-39 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-12,17-39 and 33 are unclear as they refer to a glucocorticoid-induced receptor gene. It is not clear if the claims are meant to encompass all genes that are inducible by glucocorticoids (see page 1, lines 29-30) or if they are referring to genes with a specific homology and functional similarity to the glucocorticoid-induced receptor encoded by SEQ ID NO.1, or if only the gene encoded by SEQ ID NO.1 is meant to be encompassed. Clarification is necessary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claims 5-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (*Scientific American*, 1994, vol. 270, pp 34-41) in view of Harrigan (1991, Molec. Endocrinol., Vol. 5, pages 1331-1338).

Capecchi taught transforming a cell with a nucleic acid construct comprising a disruption in the HoxA-3 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous HoxA-3 locus, and using said cell to generate a mouse whose genome comprises a disruption in the HoxA-3 gene. Capecchi differs from the claimed invention in that the targeting construct does not disrupt the glucocorticoid-induced receptor gene.

However, at the time the claimed invention was made, Harrigan taught the cloning of the mouse glucocorticoid-induced receptor gene (Figure 3; GenBank Accession No. M80481).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make cells and a knockout mouse having a disruption in a targeted gene as taught by Capecchi wherein the gene was the glucocorticoid-induced receptor gene as taught by Harrigan. One of ordinary skill in the art would have been sufficiently motivated to replace the Hox3A gene with the glucocorticoid-induced a receptor gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse. One of ordinary skill in the art would have been sufficiently motivated to disrupt the glucocorticoid-induced receptor gene to determine its role in mediating the "pleiotropic responses of T-lymphocytes to glucocorticoids", as described by Harrigan (page 1331, paragraph bridging columns 1 and 2; page 1336, last paragraph).

Note that absent any phenotypic requirements for the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention. Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning gene and the manifestation of disease (page 41, column 2, 2nd full paragraph).

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

2) Claims 5-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beach (*1999, USPN 5,919,997*) in view of Harrigan (1991, Molec. Endocrinol., Vol. 5, pages 1331-1338).

Beach taught transforming a cell with a nucleic acid construct comprising a disruption in the INK4 gene, resulting in an inactivating insertion of a selective marker gene into the

endogenous INK4 locus, and using said cell to generate a knockout mouse whose genome comprises a disruption in the INK4 gene (column 14, lines 61-66). Beach taught administering compounds to the transgenic knockout mice comprising a disruption in the INK4 gene to screen for agents that affect the INK4 mutant phenotype and modulate the expression or function of INK4 (column 26, lines 51-54 and claim 11). Beach differs from the claimed invention in that the targeting construct does not disrupt the glucocorticoid-induced receptor gene.

However, at the time the claimed invention was made, Harrigan taught the cloning of the mouse glucocorticoid-induced receptor gene (Figure 3; GenBank Accession No. M80481). Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make cells and a knockout mouse having a disruption in a targeted gene as taught by Beach wherein the gene was glucocorticoid-induced receptor as taught by Harrigan and to use said animals to screen for compounds that modulate glucocorticoid-induced receptor expression or function by assessing changes in the glucocorticoid-induced receptor mutant phenotype. One of ordinary skill in the art would have been sufficiently motivated to replace the INK4 gene with the glucocorticoid-induced receptor gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse and to use the mouse to screen for agents that affects or ameliorates a mutant phenotype. One of ordinary skill in the art would have been sufficiently motivated to disrupt the glucocorticoid-induced receptor gene to screen for modulators of glucocorticoid-induced receptor expression or function as a means of identifying drugs that treat the phenotypes associated with loss of glucocorticoid-induced receptor function. Furthermore, in the process of screening for modulators of the glucocorticoid-induced receptor, it is conceivable that one would reveal the identity of the ligand to this receptor, which was also an art recognized goal (Harrigan, page 1337, column 1, lines 6-9).

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

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